

**REMARKS**

Claims 32-82 are currently pending in the Application. Claims 32-34, 36, and 39-82 are under examination. In the Final Office Action mailed June 24, 2009, the Examiner maintained several rejections, which for clarity are listed below in the order in which they are addressed herein:

1. Claim(s) 32,34,35,37-41,48-54,57,60,61,63-65,72-75,76-78, 81, and 82 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford *et al.* J Mol Diagn. 2000 May;2(2):97-104) in view of Lane *et al.* (U.S. 5,770,365), in view of Prudent *et al.* (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando *et al.* (U.S. 5,593,835), and in view of Lau *et al.*, Science. 26 October 2001. Vol. 294: Pages 858-862),
2. Claim(s) 33, 36, 44-47,58,59,62, and 68-71 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Morris *et al.*, J Clin Microbiol. 1996 Dec;34(12):2933-6),
3. Claim(s) 42, 43, 66, and 67 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Marras *et al.* "Multiplex detection of single-nucleotide variations using molecular beacons" Genet Anal. 1999 Feb;14(5-6): 151-6), and
4. Claim(s) 55, 56, 79, and 80 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Hyldig-Nielsen *et al.* (U.S. 5,985,563).

**The Claims Are Not Obvious**

1. Claim(s) 32,34,35,37-41,48-54,57,60,61,63-65,72-75,76-78, 81, and 82 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford *et al.* J Mol Diagn. 2000 May;2(2):97-104) in view of Lane *et al.* (U.S. 5,770,365), in view of Prudent *et al.* (U.S. 5,985,557), in view of Rather (U.S. 5,858,367), in view of Rando *et*

*al.* (U.S. 5,593,835), and in view of Lau *et al.*, Science. 26 October 2001. Vol. 294: Pages 858-862).

As the Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that an Examiner make “a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.” *See In re Wada and Murphy*, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Section 904 of the MPEP instructs Examiners to conduct an art search that covers “the invention *as described and claimed*.” (emphasis added). Lastly, Applicants respectfully direct attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See In re Wada and Murphy*, *citing CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 32 and 57 are amended to recite use of a first and a second hairpin probe, and the formation of an RNA detection structure in which the microRNA and the first and second hairpin probes form a dumbbell structure. Support for this amendment is found throughout the specification. For example, the double-loop “dumbbell” configuration of the miRNA/probe complex is discussed, *e.g.*, at page 24, in the second paragraph of section I, and is diagrammed, *e.g.*, in Figures 2, 24, and 25. Discussion of

modifying the RNA detection structure with nucleic acid modifying enzymes such as polymerase and/or ligase, is disclosed, *e.g.*, in the last full paragraph on page 7; modification of the structure with 5' nucleases (*e.g.*, Cleavase enzymes in Invader assays) is provided in each of Examples 1-14, and is also disclosed at page 24, in the second paragraph of section I. Claims 72, 81, and 82 are cancelled without prejudice.

As explained in the specification, one of the special difficulties in detecting small nucleic acids such as microRNAs is that they are generally too small for routine application of standard molecular biological methods (page 2, last paragraph). An inventive solution disclosed in this application comprises the formation of a detection complex in which a probe comprising a duplex region is hybridized to the microRNA. As pointed out on page 24, such dumbbell structures create a larger region of double-stranded nucleic acid by extending the ends of the miRNA with a double-stranded region of oligonucleotide. The structures can also be configured to such that the probe duplex and the probe-RNA duplex co-axially stack (see, *e.g.*, part B of Example 8 on page 57, and Example 11).

The use of two hairpin-containing probes to form a dumbbell structure has beneficial effects that are not suggested by the cited art. For example, Figures 18 and 19 diagram several different test structures and compare the reaction performance and temperature optima for each configuration. The experiments are described in Example 8. The data from these comparisons show that the use two hairpin oligonucleotides in a dumbbell structure raises the temperature optimum of the reactions and can significantly improve performance as measured by accumulate fluorescence (compared to designs with one or no hairpins).

Neither Ledford nor Lane teach or suggest formation of an RNA detection structure in which the microRNA and the first and second hairpin probes form a dumbbell structure. Lau discloses microRNAs in general but does not cure the deficiencies of the combination of Ledford and Lane, as Lau does not teach or suggest the use of hairpin probes, nor formation of an RNA detection structure comprising two hairpin probes and the microRNA. Prudent discloses detection of RNA using DNA probes. Rather outlines Northern blot procedures for RNA detection using DNA probes,

and Rando teaches aspects of RNA-DNA heteroduplexes. None of Prudent, Rather or Rando teach or suggest the use of two hairpin probes, or formation of an RNA detection structure in which microRNA and the first and second hairpin probes form a dumbbell structure. As such, the deficiencies of the combination of Ledford, Lane and Lau are not cured by the combination of any or all with the teachings of Prudent, Rather and *Rando*.

While Applicants do not acquiesce that other conditions necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Ledford, Lane and Lau does not teach or suggest all the elements of Claims 32 and 57, or the claims depending therefrom, *i.e.*, Claims 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-75, 76-78, 81, and 82. The cited art therefore fails to establish prima facie obviousness of these claims and Applicants respectfully request that these rejections be withdrawn.

2. Claim(s) 33, 36, 44-47, 58, 59, 62, and 68-71 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Morris.

Applicants discuss the shortcomings of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando above. Morris discloses a TaqMan RT-PCR assay comprising use of a fluorescent probe configured for FRET detection. Morris fails to cure the deficiencies of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando. As discussed above, Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the microRNA and the first and second hairpin probes form a dumbbell structure. Morris does not teach or suggest does not teach or suggest the use of hairpin probes, nor formation of an RNA detection structure comprising two hairpin probes and the microRNA. Thus, the combination of Ledford, Lane, Lau, Prudent, Rather, Rando and Morris fails to teach each element of Claims 33, 36, 44-47, 58, 59, 62, and 68-71, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

3. Claim(s) 42, 43, 66, and 67 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Marras.

Applicants discuss the shortcomings of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando above. Marras teaches the use of multiplex reactions to detect dingle-nucleotide variations using molecular beacon probes. Marras fails to cure the deficiencies of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando. As discussed above, Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the microRNA and the first and second hairpin probes form a dumbbell structure. Marras does not teach or suggest does not teach or suggest the use of hairpin probes, nor formation of an RNA detection structure comprising two hairpin probes and the microRNA. Thus, the combination of Ledford, Lane, Lau, Prudent, Rather, Rando and Marras fails to teach each element of Claims 42, 43, 66, and 67, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

4. Claim(s) 55, 56, 79, and 80 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford in view of Lane, in view of Prudent, in view of Rather, in view of Rando, and in view of Lau, and in further view of Hyldig-Nielsen.

Applicants discuss the shortcomings of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando above. Hyldig-Nielsen discloses the detection of ribosomal RNA using peptide nucleic acid probes. Hyldig-Nielsen fails to cure the deficiencies of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando. Hyldig-Nielsen fails to cure the deficiencies of the combination of Ledford, Lane, Lau, Prudent, Rather and Rando. As discussed above, Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the microRNA and the first and second hairpin probes form a dumbbell structure. Hyldig-Nielsen does not teach or suggest does not teach or suggest the use of hairpin probes, nor formation of an RNA detection structure comprising two hairpin probes and the microRNA. Thus, the combination of Ledford, Lane, Lau, Prudent, Rather, Rando and Hyldig-Nielsen fails to teach each element of Claims 55, 56,

79 and 80 and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

## **CONCLUSION**

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at 608-662-1277.

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